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Facile Synthesis of 2-Arylphenols via Palladium-Catalyzed Cross-Coupling of Aryl Iodides with 6-Diazo-2-cyclohexenones

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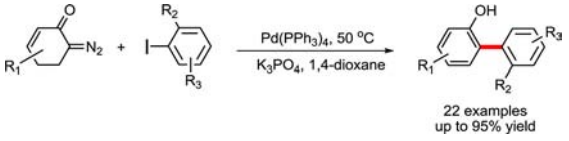
ABSTRACT



2-Arylphenols were conveniently synthesized from aryl iodides and 6-diazo-2-cyclohexenones, in moderate to excellent yields, via tandem Pd-catalyzed cross-coupling/aromatization. The preliminary results for the corresponding enantioselective version showed that the coupling products could be generated in up to 72% ee.

Owing to the ubiquity of biaryl scaffolds in ligands, natural products, and pharmaceutical agents, great endeavors have been devoted to the synthesis of these molecules.[1] Generally, biaryl compounds are prepared either by cross-coupling reactions of two aryl synthons (Scheme 1, eq 1) or by oxidative aromatization of an aryl substituted cyclohexadiene or its equivalent (Scheme 1, eq 2). Furthermore, currently available protocols[2] for obtaining optically active biaryls are limited to resolution of the corresponding racemates, ligand-catalyzed reactions, and auxiliary-controlled asymmetric synthesis. However, these methods each have their respective drawbacks. For instance, in the case of resolution, a maximum yield of 50% can only be expected for each enantiomer. Substrate dependence or troublesome removal of the chiral auxiliaries can be problematical in the remaining methods mentioned above. Therefore, there remains an urgent need to develop alternative efficient syntheses of biaryl compounds, especially asymmetric syntheses.

Pd-catalyzed cross-coupling reactions of diazo compounds have attracted considerable attention over the past decade.[3,4] Although many results have been reported, especially the enlightening synthesis of α,β-unsaturated ketones from α-diazoketones by Wang and co-workers,[3g] to the best of our knowledge, the synthesis of biaryls from diazo compounds has not been reported yet. Herein, we wish to present a new Pd-catalyzed cross-coupling/aromatization

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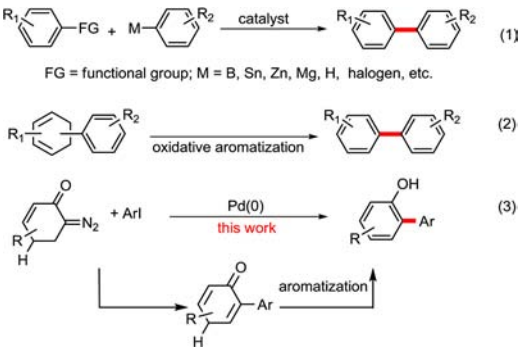
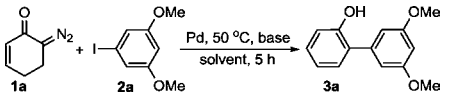
Scheme 1. Previous Syntheses of Biaryls and a New Approach to 2-Arylphenols



approach for the synthesis of 2-arylphenols from aryl iodides and 6-diazo-2-cyclohexenones (Scheme 1, eq 3). In addition, some optically active arylphenols were synthesized from 5-substituted 6-diazo-2-cyclohexenones through a point-to-axial chirality transfer strategy.

We started our investigations by examining the coupling reaction between diazo compound **1a** and aryl iodide **2a**, in the presence of Et_3N (3 equiv) and $Pd(PPh_3)_4$ (10 mol %) in 1,4-dioxane at 50 °C for 5 h, and the reaction afforded biaryl **3a** in 33% yield (Table 1, entry 1). We subsequently screened the reaction conditions, such as the bases, molar ratios of **1a** to **2a**, and solvents. Various bases were carefully tested. Comparable product yields (47−54%) were obtained when Et_3N, K_2CO_3, Li_2CO_3, KOAc, or CsF was used as the base (entries 2−6), while using stronger bases such as Cs_2CO_3 and *t*-BuOK resulted in lower yields of the product (entries 7 and 8). In the case of $K_3PO_4 \cdot 3H_2O$ chosen as the base, the yield of **3a** was further enhanced to 66−70% (entries 9 and 10). An excellent yield (92%) was achieved when anhydrous K_3PO_4 was employed as the base instead of $K_3PO_4 \cdot 3H_2O$, while the molar ratio of **1a**/**2a** was maintained at 2.1:1 (entry 11), demonstrating that the presence of even a trace amount of water could be detrimental to the reaction. Solvent-screening experiments showed that the reaction proceeded less effectively in toluene or THF (entries 14 and 15) compared with the one in dioxane. Lower yields (21−50%) were obtained when the reaction was conducted in CH_3CN or DCE (entries 16 and 17). Lower catalyst loading led to decreased product yield (entry 18). In addition, when $Pd_2(dba)_3$ was used as the precatalyst, only a complex mixture was generated.

Table 1. Optimization of the Reaction Conditions[a]



entry	**1a**:**2a**	base	solvent	yield[b] (%)
1	1:1	Et_3N	1,4-dioxane	33
2	1.1:1	Et_3N	1,4-dioxane	50
3	1.1:1	K_2CO_3	1,4-dioxane	50
4	1.1:1	Li_2CO_3	1,4-dioxane	52
5	1.1:1	KOAc	1,4-dioxane	54
6	1.1:1	CsF	1,4-dioxane	47
7	1.1:1	Cs_2CO_3	1,4-dioxane	22
8	1.1:1	*t*-BuOK	1,4-dioxane	11
9	1.1:1	$K_3PO_4 \cdot 3H_2O$	1,4-dioxane	66
10	2.1:1	$K_3PO_4 \cdot 3H_2O$	1,4-dioxane	70
11	**2.1:1**	**K_3PO_4**	**1,4-dioxane**	**92**
12	1.5:1	K_3PO_4	1,4-dioxane	82
13[c]	2.1:1	K_3PO_4	1,4-dioxane	73
14	2.1:1	K_3PO_4	toluene	76
15	2.1:1	K_3PO_4	THF	80
16	2.1:1	K_3PO_4	CH_3CN	21
17	2.1:1	K_3PO_4	DCE	50
18[d]	2.1:1	K_3PO_4	1,4-dioxane	85

[a] Reaction conditions: **2a** (0.25 mmol), $Pd(PPh_3)_4$ (10 mol %), base (3 equiv), solvent (4 mL). [b] Isolated yield. [c] K_3PO_4 (1.1 equiv). [d] $Pd(PPh_3)_4$ (5 mol %).

With the optimized reaction conditions in hand, we next examined the scope of the current Pd-catalyzed cross-coupling/aromatization protocol. An array of aryl iodide/6-diazo-2-cyclohexenone combinations were subjected to the optimized conditions, and the results are summarized in Table 2.[5] In general, different 6-diazo-2-cyclohexenones were found to couple smoothly with **2a** or **2b** to give the corresponding biaryls in decent yields (entries 1−6). The substituents on the 6-diazo-2-cyclohexenones did not dramatically affect the reaction yield, although 5-substituted 6-diazo-2-cyclohexenones required much longer reaction times (entries 3 and 4). When ester **2b** was used as a substrate, lactonized biaryls **3f** and **3g** were obtained in excellent yields (entries 5 and 6). When **1a** was used as the diazo substrate, iodobenzenes bearing with either electron-donating or electron-withdrawing groups

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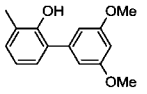
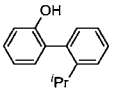
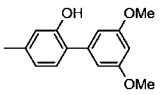
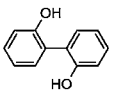
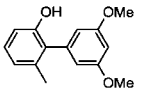
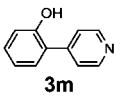
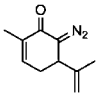
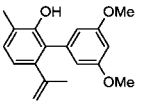
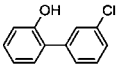
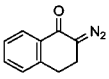
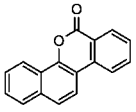
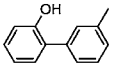
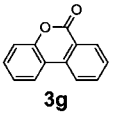
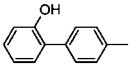
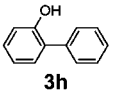
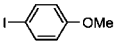
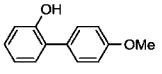
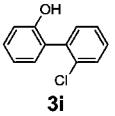
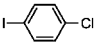
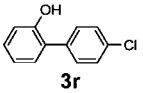
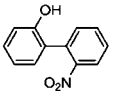
(4) For recent reviews, see: (a) Zhang, Y.; Wang, J. *Eur. J. Org. Chem.* **2011**, 1015. (b) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013** DOI: 10.1021/ar300101k.

(5) (a) While **1b**−**g** could be stored at −20 °C for two months without appreciable decomposition, **1a** was relatively less stable. Even when **1a** was stored at −20 °C for two days, an unidentified new compound could be detected. (b) In all cases, $Pd(PPh_3)_4$ was used as freshly prepared. It was found that even a trace amount of Pd(II) could lead to a decrease of the yields of the desired coupling products. For Pd(II)-mediated polymerization of diazoacetates, see: Ihara, E.; Haida, N.; Iio, M.; Inoue, K. *Macromolecules* **2003**, *36*, 36.

Table 2. Palladium-Catalyzed Cross-Coupling/Aromatization Reactions of Aryl Iodides with 6-Diazo-2-cyclohexenones[a]

entry	diazo (**1**)	ArI (**2**)	time (h)	product	yield (%)[b]	entry	diazo (**1**)	ArI (**2**)	time (h)	product	yield (%)[b]
1	 **1b**	**2a**	5	 **3b**	95	10[c]	**1a**	 **2f**	38	 **3k**	85
2	 **1c**	**2a**	5	 **3c**	92	11	**1a**	 **2g**	36	 **3l**	64
3	 **1d**	**2a**	24	 **3d**	93	12	**1a**	 **2h**	38	 **3m**	54
4	 **1e**	**2a**	22	 **3e**	95	13	**1a**	 **2i**	10	 **3n**	73
5	 **1f**	 **2b**	6	 **3f**	90	14	**1a**	 **2j**	10	 **3o**	66
6	**1a**	**2b**	4	 **3g**	93	15	**1a**	 **2k**	26	 **3p**	68
7	**1a**	 **2c**	5	 **3h**	84	16	**1a**	 **2l**	32	 **3q**	60
8	**1a**	 **2d**	7	 **3i**	64	17	**1a**	 **2m**	28	 **3r**	73
9	**1a**	 **2e**	6	 **3j**	76						

[a] Reaction conditions: **1** (0.52 mmol), **2** (0.25 mmol), K_3PO_4 (0.75 mmol), $Pd(PPh_3)_4$ (10 mol %), 1,4-dioxane (3.5 mL), 50 °C. [b] Isolated yield. [c] $Pd(PPh_3)_4$ (30 mol %), 70 °C.

at the *ortho*-, *meta*-, or *para*-position could deliver the biaryls in moderate to good yield (entries 6−17, except 12). It seems that the reaction time might be dependent upon the rate of oxidative addition of the palladium catalyst to the iodides. When iodobenzene **2f** (with a relative bulky isopropyl group at the *ortho*-position) was tested for the reaction, higher catalyst loading and higher temperatures were needed to ensure a good yield (entry 10). For the reaction of **1a** with **2g**, the TBS group was deprotected and diphenol **3l** was formed in 64% yield (entry 11). Note that light-sensitive 4-iodopyridine could also serve as an aryl iodide substrate (entry 12).

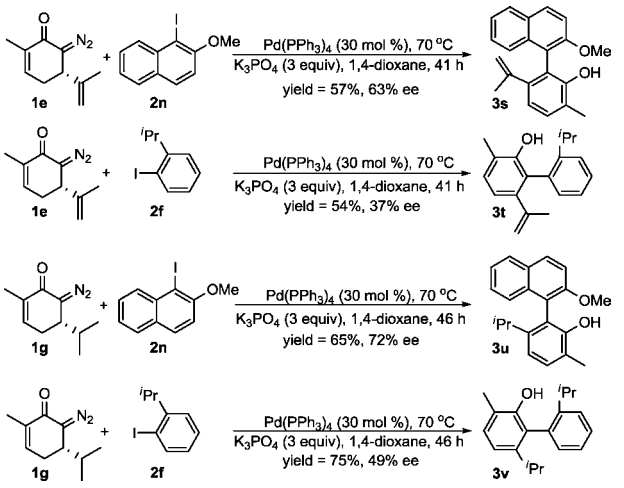
The importance of the 2-arylphenol motif in natural products is noteworthy, and the phenols can be further converted into phosphine ligands,[6a,b] phosphoric acids,[6c] and phosphoramidite ligands.[6d] We envisioned that this cross-coupling/aromatization approach might be used to synthesize optically active biaryl compounds from chiral 5-substituted 6-diazo-2-cyclohexenones[7] via point-to-axial chirality transfer.[8] Indeed, the coupling of **1e** (derived from L-(−)-carvone) with **2n** and **2f** delivered **3s** (63% ee) and **3t** (37% ee), respectively (Scheme 2). Use of sterically more bulky isopropyl-substituted substrate **1g** resulted in further

(6) (a) Uozumi, Y.; Kawatsura, M.; Hayashi, T. *Org. Synth.* **2004**, *10*, 363. (b) Liu, L.; Wu, H.; Yu, J. *Chem.—Eur. J.* **2011**, *17*, 10828. (c) Jacques, J.; Fouquey1, C. *Org. Synth.* **1993**, *8*, 50. (d) Smith, C. R.; Mans, D.; RajanBabu, T. V. *Org. Synth.* **2008**, *85*, 238.

(7) For the synthesis of enantiomerically pure 5-substituted 2-cyclohexenones, see: Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811.

(8) For an example of point-to-axial chirality transfer in synthesis of axially chiral allenes, see: Ohmiya, H.; Yokobori, U.; Makida, Y.; Sawamura, M. *Org. Lett.* **2011**, *13*, 6312.

Scheme 2. Chirality Transfer Experiments

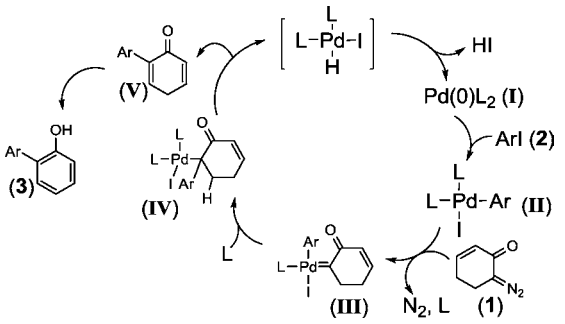


improvement in the ee value of 2-arylphenol products (72% ee for **3u**; 49% ee for **3v**).

A plausible mechanism for the coupling/aromatization reaction is proposed in Scheme 3, which is similar to that reported by Wang.[3g] The process presumably starts with oxidative addition of aryl iodide **2** to Pd(0) catalyst **I** to give complex **II**, which reacts with diazo compound **1** and forms palladium−carbene complex **III**. Migratory insertion of the aryl group produces intermediate **IV**, β-elimination of which provides **V** and the eventually regenerated Pd(0) catalyst **I**. Intermediate **V** rapidly isomerizes to afford 2-arylphenol **3** via aromatization.

In summary, we have developed a new synthesis of 2-arylphenols from aryl iodides and 6-diazo-2-cyclohexenones through tandem Pd-catalyzed cross-coupling/aromatization. A wide range of aryl iodides have been tested in this reaction, which gave the biaryl products in

Scheme 3. Proposed Mechanism



moderate to excellent yields. Preliminary results on an asymmetric version of the reaction indicated the possibility of point-to-axial chirality transfer, which provides a new promising approach to preparing chiral biaryl ligands from the corresponding ketones. Further improvement and applications in chiral biaryl ligands synthesis are in progress.

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Supporting Information Available. Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.